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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,620	03/15/2002	Michael P. DeNinno	PC11066AAKM	2274

7590 10/27/2003

Gregg C. Benson
Pfizer Inc.
Patent Department, MS 4159
Eastern Point Road
Groton, CT 06340

EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/099,620	Applicant(s) DiNinno et al.
	Examiner L. E. Crane	Group Art Unit 1623

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--03--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on **-07/12/02** (IDS)-.

[] This action is **FINAL.**

[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims ---1-23--- are pending in the application. Claims -[]- have been cancelled.
Of the above claim(s) ---[]--- is/are withdrawn from consideration.

[] Claim(s) ---[]--- is/are allowed.

[X] Claims ---1-23--- are rejected.

[] Claim(s) ---[]--- is/are objected to.

[] Claim(s) ---[]--- are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[] The proposed drawing correction, filed on -[]- are [] approved [] disapproved.

[] The drawing(s) filed on -[]- is/are objected to by the Examiner.

[] The specification is objected to by the Examiner.

[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).

[] All [] Some* [] None of the CERTIFIED copies of the priority documents have been

[] received.

[] received in Application No. (Series Code/Serial Number) -[]-.

[] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: -[]-.

Attachment(s)

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). **--04--**

[X] Notice of Reference(s) Cited, PTO-892

[] Notice of Draftsperson's Patent Drawing Review, PTO-948

[] Interview Summary, PTO-413

[] Notice of Informal Patent Application, PTO-152

[] Other: -[]-.

No claims have been cancelled and no preliminary amendments filed as of the date of the instant Office action. An Information Disclosure Statement (IDS) filed July 12, 2002 has been received with all cited references and made of record.

Claims **1-23** remain in the case.

Claim **22** is objected to because of the following informalities:

In claim **22** at the last line, the terms within the term "a Na/Ca exchanger modulators" fails to agree on grammatical number. Did applicant intend the term to read -- a Na/Ca exchanger modulator --.

Appropriate correction is required.

Claims **1-13** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description standard of Regents of the University of California v. Eli Lilly (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)); see MPEP §2163 at page 2100-162, column 1. Applicant is requested to note that the examples of the instant disclosure are limited to 3-deoxy-3-aminoribouronic acid and amide compounds, and does not describe any other 5-functionality in place of carboxyl or carboxamide or any alternative membered ring in place of ribofuranosyl (variable X = O). Therefore, the noted claims are deemed to lack adequate written description in support of the full scope of embodiments of the instant noted claims. The same argument applies

to the excessive breadth of the definitions of variables G, R^4, and " R^4 and R^5 " taken together.

Claims **1-13** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is excessive, specifically because of the presence in claims **1-6** of the definitions of variables X, Z, R^1, B, G, R^4, R^4 and R^5 taken together, and R^{B1}-R^{B5}, and the total absence of any test data in support of method claims **7-11**.

B. The nature of the invention is directed to analogues of purine nucleosides, phamaceutical compositions thereof, final steps in the process of making said analogues, and a method of reducing tissue damage caused by ischemia or hypoxia by administration of said analogues to a host in need thereof.

C. The state of the prior art is well developed. There are numerous other closely related purine nucleoside analogues which are known in the art to mimic the capability of adenosine to limit the deliterious effects of ischemia or hypoxia.

D. The level of one or ordinary skill is high, an understanding of organic synthesis of nucleosides, and the pharmacology of adenosine analogs being required to practice the instant claimed invention.

E. The level of predictability in the art is fairly high in the treatment of whole living hosts, there being numerous examples in the prior art wherein adenosine and analogues thereof (NECA, etc.) have been used to assist in the mitigation of tissue damages known to result from ischemia and/or hypoxia, e.g. in hearts an other organs in the process of transport between hosts. However, the minimization of damage caused by ischemia/hypoxia in living tissue during storage and/or transport between living hosts (transplantable organs, etc.) is much less well understood and therefore much less predictable.

F. The amount of direction provided by the inventor includes detailed directions for the synthesis of a substantial list of potential active ingredients, but fails to provide a single example wherein actual testing has substantiated the alleged pharmacological activity of any single compound synthesized.

G. The existence of working examples is limited to chemical synthesis of potential active ingredients.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deminimus concerning the chemical synthesis of the specific embodiments, but increases to an unacceptable level when the un-enabled variables and/or un-enabled the additional layers upon layers of substitution found in the definitions of X, Z, R^1, B, G, R^4, R^4 and R^5 taken together, and R^{B1}-R^{B5} are considered. Attention is drawn in particular to the laundry lists of substituents within the definitions of variables R^1, G, R^4, R^5, and R^4 and

R^5 taken together, wherein nearly all of these listed substituents have not been enabled by even a single embodiment. In addition, the total absence of any test data to establish that the instant claimed compounds are predictably active in line with the content of the prior art means that the claims directed to methods of treating and pharmaceutical compositions are entirely lacking in enabling support, whether the method is applied to a host already suffering from ischemia/hypoxia or is treated propylactically in anticipation thereof.

Claims **14-23** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims includes a method for treating ischemia or hypoxia induced cardiac damage by administration of pharmaceutical compositions incorporating compounds of claim **1**, and additional active ingredients including "a cardiovascular agent" selected from more than 40 specific and generic alternatives (see claims **17, 18 and 22**), "a glycogen phosphorylase inhibitor" selected from 15 alternative compounds (claim **21**), "a sorbitol dehydrogenase inhibitor," and "an aldose reductase inhibitor" selected from two alternatives (claim **20**). Also claim **23** is directed to kits incorporating a unit

dosage of a compound of claim **1**, a choice of the second active ingredients of claim **17** in unit dosage forms, and a container.

B. The nature of the invention is directed to the treatment of ischemia or hypoxia induced cardiac damage by administration of pharmaceutical compositions incorporating compounds of claim **1**, and a second active ingredient as listed in claim **17**.

C. The state of the prior art includes compounds which read on the subject matter of claim **1** but aside from applicant's own work (PTO-1449 ref. **AN**), do not include the option of a second active ingredient as described in claims **17, 18 and 22** or the treatment of hypoxia/ischemia-induced damage in cardiac tissue.

D. The level of one or ordinary skill is relatively high, the practice of the instant claimed subject matter requiring knowledge of how to synthesize 3'-deoxy-3'-amino-purine nucleosides and the medical details of how to effectively administer said compounds alone or in combination with other medicinal substances.

E. The level of predictability in the art is relatively high when a single adenosine-isosteric compound is being administered to treat cardiac/circulatory tissue for a variety of aliments including tissue/organ damage caused by poor or interrupted blood circulation. However, the execution of such a treatment in the *in vivo* presence of a second active ingredient selected from the vast array of alternatives listed in claim **17** and subsequent claims is not well known in the art outside of applicant's own work (see ref. **AN**) and is therefore highly unpredictable.

F. The amount of direction provided by the inventor is limited to the administration of compounds of claim **1** *in vitro* to determine a

range of binding constants at the adenosine A_3 binding site in the last paragraph of page 92 with no experimental details provided. There are no specific examples wherein the effects of simultaneous administration of the compounds of claim **1** with any second active ingredient of claim **17** is disclosed, nor is there any disclosure of any real or potential adverse side effects of such concomitant administrations.

G. The existence of working examples is limited as noted in the previous paragraph.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be undue for the noted claims because neither the advantageous effects nor the adverse effects of simultaneous administration of a compound of claim **1** and a second active ingredient of claim **17** have been provided to guide the ordinary practitioner in the practice of the instant claimed method of treatment.

Claims **1 and 2** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **1** at line 11, the term "carbamoyl" is both incomplete and indefinite. The functional group "O-carbamoyl" is -- H_2N-C(=O)-O- --. Carbamoyl may be attached to another molecule by either nitrogen or one of the oxygen substituents, but if attachment is through nitrogen, then the oxygen must be alkylated or arylated, or otherwise substituted in order for the resultant structure to be stable (carbon dioxide easily produced otherwise). The noted terms fail to specify which atom (O or N) is attached to the ribofuranose ring at the R^1 substituent location,

and also how the other atom is substituted, thereby rendering the noted terms incomplete. In addition all of the exemplifications have a carbon but do not have either a nitrogen or an oxygen attached as R^1 at C-4 of the furanose ring, suggesting that applicant may have intended to define R^1 as -- N,N-dialkylcarbamoyl**methyl** -- (RR'N-(C=O)-O-$\mathbf{CH_2}$-) or the like. As an extension of the rejection supra under 35 U.S.C. §112, first paragraph, examiner's inspection of the disclosure found no exemplifications wherein applicant has disclosed compounds so substituted.

In claim **1** at line 15, the variable "A" defined as " -(C_mH_{2m-2})- " is too abbreviated and therefore fails to particularly point out what is being claimed. Applicant is respectfully requested to amend the instant claim to indicate that the noted formula is directed to -- either a monocyclic or monounsaturated linker moiety -- .

In claim **1** at lines 19, 21 and 58-59, the term "optionally linked through (C_1-C_3)alkyl" is unclear because the claim has not defined what atom of the previous listed "ring" substituent is being linked to what other atom of said "ring" substituent or to what atom of Formula **(I)**.

In claim **1** at lines 66-68, the proviso provided is read by examiner to exclude applicant's prior disclosure exemplified in the instant record by **Pfizer '399** (PTO-1449 ref. **AN**). In order to insure that the last two lines of the claim are read to apply to the subject matter of lines 1-65 of said claim and not only to the subject matter of lines 66-68, examiner respectfully requests that applicant move this proviso to the very end of the claim.

In claim **2** at line 5, the term "(C_1-C_6)alkylcarbamoyl" is rejected for the same reasons stated in the immediately preceding rejection.

Additionally, because claim **1** only specifies "carbamoyl" the instant noted term is lacking in proper antecedent basis in claim **1**. The noted term also renders said claim incomplete for failure to specify which heteroatom(s) (O or N or both) is alkylated.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims **1-6** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Baker et al. '505** (PTO-892 ref. **A**).

Applicant is referred to **Baker et al. '505** at columns 17-18, Example 40, which is directed to a compound which reads on the instant claims.

PTO-892 references **B** (Ex. 20 at col. 11) **S and T** disclose the identical compound.

Claims **1-6 and 12-13** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Goldman et al.** (PTO-892 ref. **T**).

Applicant is referred to the paragraph bridging pages 4174-4175 wherein the N^6-benzylamino compound and the reports of biological activity read on the instant noted claims.

PTO-892 ref. **S** makes a similar anticipatory disclosure.

Claims **1-13** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Jacobson et al. '774** (PTO-1449 ref. **AB**).

Applicant is referred to the instant references at claims ***1, 9 and 13*** wherein the instant claimed subject matter is either clearly anticipated (claims **1-6 and 12-13**) or taught therein (claims **7-11**). See column 12, lines 54-58 which discloses the general utility of adenosine A_3 receptor agonists in the treatment of a variety of disease conditions including ischemia resulting for a variety of different medical conditions including strokes and cardiac arrest.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-13** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Jacobson et al. '774** (PTO-1449 ref. **AB**).

The instant claims are directed to 3'-deoxy-3'-amino-6-substituted aralkylamino purine nucleoside-5'-uronamide analogues, pharmaceutical compositions thereof, and methods of treatment wherein the adenosine A_3 receptor activation effects are claimed to have the effect of reducing the tissue damage resulting from ischemia or hypoxia which typically accompany the incidental (e.g. heart attack or stroke) or intentional

(organ transplant induced) interruption of blood flow in a mammalian host.

Jacobson et al. '774 discloses compounds, pharmaceutical compositions, and methods of treatment wherein the adenosine A_3 receptor is activated.

Jacobson et al. '774 does not expressly claim the treatment of tissue damage induced by hypoxia or ischemia, but at column 12, lines 54-58 does disclose the general utility of adenosine A_3 receptor agonists including those specifically disclosed by this reference in the treatment of a variety of disease conditions including ischemia resulting from a variety of different medical conditions including strokes and cardiac arrest.

In view of the explicit teachings of the cited reference, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to presume that the compounds and pharmaceutical compositions of **Jacobson et al.** would be effective in the treatment of the consequences of medical and/or surgical events which induce ischemia and/or hypoxia.

Therefore, the instant claimed compounds, pharmaceutical compositions and methods of treatment would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Claims **14-23** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner

presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

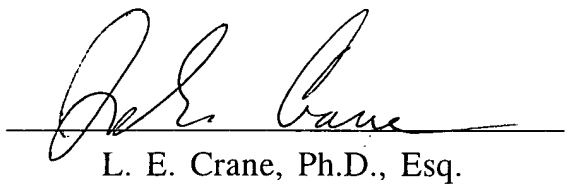
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O, Wilson, can be reached at (703)-308-4624.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

Art Unit 1623

LECrane:lec
10/23/03



L. E. Crane, Ph.D., Esq.
Patent Examiner
Technology Center 1600